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Review

Seasonal and post-trauma remodeling in cone-dominant ground squirrel retina

Dana K. Merriman [a], [*], Benjamin S. Sajdak [b], Wei Li [c], Bryan W. Jones [d]

[a] Department of Biology, University of Wisconsin Oshkosh, Oshkosh, WI, USA
[b] Department of Cell Biology, Neurobiology, & Anatomy, Medical College of Wisconsin, Milwaukee, WI, USA
[c] Unit on Retinal Neurobiology, National Eye Institute, Bethesda, MD, USA
[d] Department of Ophthalmology & Visual Science, University of Utah School of Medicine, Salt Lake City, UT, USA

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ABSTRACT

With a photoreceptor mosaic containing ~85% cones, the ground squirrel is one of the richest known mammalian sources of these important retinal cells. It also has a visual ecology much like the human's. While the ground squirrel retina is understandably prominent in the cone biochemistry, physiology, and circuitry literature, far less is known about the remodeling potential of its retinal pigment epithelium, neurons, macroglia, or microglia. This review aims to summarize the data from ground squirrel retina to this point in time, and to relate them to data from other brain areas where appropriate. We begin with a survey of the ground squirrel visual system, making comparisons with traditional rodent models and with human. Because this animal's status as a hibernator often goes unnoticed in the vision literature, we then present a brief primer on hibernation biology. Next we review what is known about ground squirrel retinal remodeling concurrent with deep torpor and with rapid recovery upon re-warming. Notable here is rapidly-reversible, temperature-dependent structural plasticity of cone ribbon synapses, as well as pre- and post-synaptic plasticity throughout diverse brain regions. It is not yet clear if retinal cell types other than cones engage in torpor-associated synaptic remodeling. We end with the small but intriguing literature on the ground squirrel retina's remodeling responses to insult by retinal detachment. Notable for widespread loss of (cone) photoreceptors, there is surprisingly little remodeling of the RPE or Müller cells. Microglial activation appears minimal, and remodeling of surviving second- and third-order neurons seems absent, but both require further study. In contrast, traumatic brain injury in the ground squirrel elicits typical macroglial and microglial responses. Overall, the data to date strongly suggest a heretofore unrecognized, natural checkpoint between retinal deafferentiation and RPE and Müller cell remodeling events. As we continue to discover them, the unique ways by which ground squirrel retina responds to hibernation or injury may be adaptable to therapeutic use.

Contents

Abbreviations: AMD, age-related macular degeneration; AOSLO, adaptive optics scanning light ophthalmoscopy; CMP, computational molecular phenotyping; CNS, central nervous system; CRALBP, cellular retinaldehyde binding protein; CRMP-2, collapsin response mediator protein 2; CtBP2, C-terminal binding protein 2; DPYSL2, dihydropyrimidinase-like 2; EAAT1, excitatory amino acid transporter 1; ERG, electroretinogram; GFAP, glial fibrillary acidic protein; GS, ground squirrel; IBA, interbout arousal; IPL, inner plexiform layer; OCT, optical coherence tomography; ONL, outer nuclear layer; OLM, outer limiting membrane; OPL, outer plexiform layer; RBM3, RNA binding motif protein 3; RD, retinal detachment; RP, retinitis pigmentosa; RPE, retinal pigment epithelium; SCN, suprachiasmatic nucleus; SRS, subretinal space; TEM, transmission electron microscopy; 13LGS, thirteen-lined ground squirrel.

[*] Corresponding author. Biology-UW Oshkosh, Oshkosh, WI 54901-8640, USA.

E-mail addresses: merrimad@uwosh.edu (D.K. Merriman), besajdak@mcw.edu (B.S. Sajdak), liwei2@nei.nih.gov (W. Li), bryan.jones@m.cc.utah.edu (B.W. Jones).

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1. Introduction

The ground squirrel (GS) photoreceptor mosaic contains ~85% cones, including a large, nearly pure-cone region near the posterior pole (Kryger et al., 1998; Long and Fisher, 1983; Sakai et al., 2003). Even those GS species that are smaller than rats have eyes that are substantially larger than the rat's. These features combine to make the GS a rich source of mammalian cones and the circuitry underlying their function. Hence, GS retina has been invaluable for landmark cone discoveries including outer segment morphogenesis (Steinberg et al., 1980), disc shedding (Anderson et al., 1978; Long et al., 1986), retinoid binding proteins (Anderson et al., 1986), glucose metabolism (Winkler et al., 2008), and visual transduction (Mata et al., 2002; von Schantz et al., 1994; Wang and Kefalov, 2011; Weiss et al., 1998).

Since cone damage is catastrophic for human vision, it is somewhat surprising how seldom the GS has been used to model injury responses, including retinal remodeling. Some of this is likely due to its status as a wild animal, though captive breeding of one species is possible (Merriman et al., 2012). As this review will describe, what limited information we have suggests that photoreceptor loss from the GS retina results in rather different downstream responses relative to what has been recorded in other animal models and indeed in humans.

We begin this review by briefly reviewing the GS visual system. We then overview GS hibernation and what is currently known about retinal remodeling as a seasonal phenomenon. We end by considering GS retinal remodeling after experimental insult. Given the relative underutilization of this model species, more questions are raised than answers provided. Where relevant, studies of other parts of the GS central nervous system are referenced.

2. Ground squirrel visual system

2.1. Visual ecology, life history, and genome

Ground squirrels are strictly diurnal, omnivorous rodents that routinely engage in visually-guided predation on fast-moving prey including insects, other rodents, snakes, and birds. Ground squirrels also serve as prey for agile, fast-moving predators. Favoring open short-grass habitats and bright sunny days, GSs commonly adopt an erect vigilance posture. As such, GSs share much of the human's visual ecology and thus make useful complements to traditional rat and mouse models of visual function and disease (van Hooser and Nelson, 2006).

Unlike rats or mice, GSs do not become reproductive until nearly one year of age, after their first winter hibernation (section 3.1). Wild GSs experience substantial mortality as juveniles but adults may survive 3–4 years (Michener, 1989). In our captive colony of 13LGSs, lifespan typically extends to 5–6 years. The GS's longer natural "childhood" and lifespan eases some of the scalability problems presented by traditional rodent models used in CNS damage research (Agoston, 2015).

Other assets of the GS model include the 13-lined GS genome (13LGS, *Ictidomys tridecemlineatus*, formerly *Spermophilus*, formerly *Citellus*), which was chosen for sequencing by the National Human Genome Research Institute in 2005. Currently, over 187,000 13LGS nucleotide sequences are found in GenBank. The 13LGS mitochondrial genome has also recently been sequenced (Zhang et al., 2015). The markedly slow rate of evolution of GSs makes them useful for comparative genomics *vis-à-vis* rats and mice (reviewed by Rodriguez-Ramos Fernandez and Dubielzig, 2013). A retina-specific RNAseq database with 20,000 genes has also been acquired from the 13LGS (Wei Li, unpublished).

2.2. General ocular anatomy

Ocular parameters for several species of GS are shown in Table 1. Ground squirrel eyes are set deeply and laterally within the skull, making enucleation and *in situ* access to the optic nerve more challenging than in rats or mice. The entire sclera is darkly pigmented. Their emmetropic eyes are thought to have low spherical and chromatic aberration (Sussman et al., 2011; Gur and Sivak, 1979). The GS lens is spherical, yellow, and small relative to the size of the globe (Vaidya, 1965), which facilitates intraocular manipulations of the retina. Its UV filters resemble those of human